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Dominance and Homozygosity

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Because of the high consanguinity rates in many communities in Israel we had the opportunity to study homozygosity for some dominant disorders. This experience and a review confirmed that in most cases homozygotes of dominant disorders are more severely affected than heterozygotes. In some cases molecular analysis allowed an understanding of the mechanisms involved. While heterozygosity for point mutations or deletions of PAX3 lead to similar manifestations (Waardenburg syndrome), in homozygotes the phenotype is much more severe, probably in direct relation to the loss of function. Charcot-Marie-Tooth 1A is caused by a duplication of PMP22 and further overexpression lead to a more severe disorder. In diseases in which the mutation leads to an abnormal structural protein, the homozygote may be as severely affected as the heterozygote (epidermolysis bullosa simplex) or more severely (achondroplasia, Marfan syndrome). The polyglutamine tract is translated in disorders caused by CAG triplet expansions. In homozygotes for Machado-Joseph disease the onset is earlier and the symptoms are more severe than in heterozygotes, while in Huntington disease homozygotes are affected like heterozygotes. Am. J. Med. Genet. 68:412–416, 1997.

KEY WORDS: dominance; homozygosity

INTRODUCTION

By definition, an allele that determines the phenotype of the heterozygote is dominant. However, the clinical classification is not always accurate, and disorders caused by mutations of the gene for ß-globin, such as ß-thalassemia and sickle cell anemia, are classified as recessive, even though symptoms are present in the heterozygote. The reason may be that homozygotes who are more severely affected are relatively frequent in the population as opposed to dominant hypercholesterolemia in which the heterozygote is similarly mildly affected and in which the severely affected homozygotes are rare. Indeed, in humans, homozygosity for a dominant allele is rare and often results from assortative mating or consanguinity. Therefore, most examples are reported in communities, such as those found in Israel, in which inbreeding is high. While classically a single copy of one dominant allele should result in the same degree of involvement as in the homozygous state of the gene, many examples in which the homozygotes were much more severely affected than the heterozygotes have been reported and were reviewed by Pauli [1983].

In the last few years, the molecular basis of many disorders was discovered and a framework for understanding the basis of dominance in humans was elaborated [Wilkie, 1994]. In parallel, in some autosomal dominant disorders, homozygosity was confirmed by molecular analysis and this gave additional information for the understanding of the mechanisms involved (Table I). In this discussion examples of the disorders in which the gene has been cloned are considered.

MUTATIONS CAUSING A LOSS OF FUNCTION

One often refers to haploinsufficiency when a mutation leads to the inactivation of one of the alleles. The abnormal phenotype may be caused by the imbalance with another protein, which should be in equal quantities to build a complex molecule, or by the interference with a rate-limiting step of a metabolic pathway. Another possibility is that the phenotype is caused by the reduction of the product of a regulatory gene that works close to a threshold.

PAX Genes

PAX3 gene is a transcription factor expressed in embryonic development. In humans, heterozygous mutations or deletions cause Waardenburg syndrome type I (WS1) and type III (WS3). There is little correlation between the genotype and phenotype and deletions of the entire gene result in phenotypes indistinguishable from those associated with single base substitutions in the paired domain or homeodomain [Tassabehji et al., 1995].

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TABLE I. Dominant Disorders in Which Homozygotes Have Been Reported and Confirmed by Molecular Analysis*

Disorder	Gene	Type of mutation	Additional information	Reference
True dominant				
Huntington	Huntingtin	Expansion of (CAG) repeats	Few examples	Wexler et al., 1987; Myers et al., 1989
Creutzfeldt- Jakob	Prion	G to A substitution in codon 200	Three cases from the Libyan Jewish community	Gabizon et al., 1993
Epidermolysis bullosa simplex	Keratin 5	Substitution of a conserved lysine K173N	One case in a large inbred family	Stephens et al., 1995
Familial amyloidotic polyneuropathy	TTR	Methionine to valine at position 30 of transthyretin	Two sibs	Holmgren et al., 1988
MEM1	?	Linkage	Two sibs, both infertile	Brandi et al., 1993
Homozygote more severely affected than heterozygote				
Achondroplasia	FGFR3	Missense in the transmembrane domain (G380R)	Many examples, clinically similar to thanatophoric dwarfism	Rousseau et al., 1994
Aniridia	PAX6	Compound heterozygote: nonsense mutations at codon 103 (paired domain) and 353 (C terminal PST domain)	Very severely affected	Glaser et al., 1994
Waardenburg	PAX3	Missense in exon 2 in paired box (S84F)	Very severely affected	Zlotogora et al., 1995
Charcot Marie Tooth	CMT1	Duplication	Earlier onset, more severe course	Patel and Lupski, 1994
Marfan syndrome	FBN1	Compound heterozygote: 2 different missense mutations in conserved AA	Severe form with early death from cardiac failure.	Karttunen et al., 1994
Synpolydactyly	HOXD13	Expansion of a polyalanine stretch in the amino-terminal region	Several examples severely affected	Akarsu et al., 1995; Muragaki et al., 1996
Dentatorubralpallidoluysian atrophy	DRPLA	Expansion of (CAG) repeats	One example with early onset	Sato et al., 1995
Machado-Joseph	MJD	Expansion of (CAG) repeats	Many examples with early onset and severe course	St George-Hyslop et al., 1994; Lerer et al., 1996

* Myotonic dystrophy was not included, since it is still not clear whether the disorder is truly dominant.

There have been two reports of homozygosity for WS. One was the product of an incestuous union, and the severely malformed fetus with exencephaly and arthrogryposis was aborted after prenatal diagnosis [Aymé and Philip, 1995]. No molecular data are available in this family. The other child is still living at the age of 2 years with symptoms of WS3, including severe upper limb defects and partial albinism [Zlotogora et al., 1995]. His parents had mild WS1; they were first cousins and originated from a large Palestinian Arab kindred in which many cases of classical WS1 were diagnosed. The child was homozygous for a mutation in the paired box domain [Zlotogora et al., 1995]. It may be that the homozygous state of the mutation is not lethal in early embryogenesis because the abnormal product retained some functional activity. Gene dosage has an important role in the function of PAX3 and it is probable that a threshold value is necessary for normal development. If the remaining activity in the homozygote is lower than 50% this may explain why the manifestations in the homozygote are more severe than those in the heterozygote. It is probable that homozygosity for mutations leading to the absence or to a nonfunctional product of PAX3 will lead to early death in humans and more severe manifestations such as those observed in the mouse.

Similar observations have been made for PAX6 mutations, which in heterozygosity causes eye defects, mainly aniridia. A child was born to a father with bilateral cataracts and a mother with aniridia, each of whom carried a different PAX6 mutation. The child was stillborn with anophthalmia and central nervous defects and was a compound heterozygote for the two different missense mutations in PAX6 [Glaser et al., 1994].

MUTATIONS CAUSING A GAIN OF FUNCTION

Duplication

Charcot-Marie-Tooth disease type 1A. Charcot-Marie-Tooth disease type 1A (CMT1A) is caused by a duplication in the gene *PMP22* [Patel and Lupski, 1994]. This gene encodes a peripheral myelin protein. Very high levels of mRNA were detected in the peripheral nerves of patients with CMT1A. The function of PMP22 seems to be very sensitive to gene dosage. Overexpression causes CMT1A, but a deletion of the *PMP22* gene causes hereditary neuropathy with liability to nerve pressure palsies (HNPP), another disorder of the peripheral nervous system. A homozygote for the duplication presented with an earlier onset and more severe disease, a clinical picture similar to Déjérine-Sottas disease, which, in some cases, is caused by a recessive mutation in the *PMP22* gene [Patel and Lupski, 1994].

Abnormal Structural Protein

When a mutation in the heterozygous state antagonizes the activity of the wild-type allele the phenotype is more severe than that observed for the heterozygote of a null mutation; therefore these mutations are often referred to as "dominant negative." When the mutant allele produces an abnormal protein it may disrupt the structure of the complex molecule produced by the normal protein.

Epidermolysis bullosa simplex. In a large kindred originating from an inbred community of Israel in which many individuals were affected with autosomal dominant epidermolysis bullosa simplex type Koebner, a mutation in the keratin 5 gene was demonstrated (K173N) [Stephens et al., 1995]. One of the affected individuals was homozygous for the mutation. There was no significant difference either in the clinical severity or the ultrastructural organization of the keratin intermediate filament cytoskeleton between the homozygote and the other affected relatives.

The keratin intermediate filament (KIF) cytoskeleton of epithelial cells is assembled from different keratin polypeptides, which immediately form heterodimers. A mutation in either gene encoding for the coexpressed basal cell-specific keratins K5 or K14 causes different types of the autosomal epidermolysis bullosa simplex. The mutation in keratin 5 (K173N) present in the above-mentioned family predicts a substitution of a lysine, which is conserved in evolution, suggesting that it plays an important role in KIF assembly, stability, or function. The similar phenotype of the heterozygote and homozygote suggests that levels of 50% abnormal K5 molecules, which would result in approximately 50% of abnormal heterodimers K5/K14, are sufficient for the phenotype to be expressed. Increasing the number of abnormal heterodimers, as in the case of homozygosity, does not further affect the phenotype.

Marfan syndrome. Some cases clinically suspected to be affected with homozygous Marfan syndrome have been reported; however, there has been only one case in which molecular studies were performed [Karttunen et al., 1994]. A child born to parents affected with Marfan syndrome had congenital lens luxation and long limbs and died at 4 months of congestive heart failure. The molecular analysis of the fibrillin 15 gene demonstrated a different missense mutation in each of the parents. The child was a compound heterozygote for the mutated genes, which were demonstrated to be transcribed with equal efficiency. In cell cultures the two parents had a reduced amount of microfibrils, while virtually no visible fibrils could be seen in the child's cultured fibroblasts.

Familial amyloidotic polyneuropathy. There is one report of two sibs of Swedish origin who were homozygous for a methionine to valine substitution at position 30 of transthyretin [Holgren et al., 1988]. At the age of 56, the brother had typical symptoms of familial amyloidotic polyneuropathy including polyneuropathy, gatrointestinal problems, and vitreous amyloid, while his elder sister was asymptomatic. This appears to be a true dominant disorder.

Creutzfeld-Jakob disease. Creutzfeld-Jakob disease has been reported in relatively high frequency among the Libyan Jews, a community that was relatively isolated for geographical and religious reasons. The disease is caused by a dominant mutation in the prion gene, and all the patients from this community

carry the same missense mutation. Inbreeding is high in the community, and two individuals suspected to be homozygous for the mutation and one in which the homozygosity was demonstrated by molecular analysis were reported [Gabizon et al., 1993]. No substantial differences were observed for the age of onset, clinical symtomatology, and progression of the disorder when the homozygotes were compared to the heterozygotes in the community [Gabizon et al., 1993]. The mechanism by which a mutation in the prion gene leads to a neurodegenerative disease is still unknown, but it can be learned from this observation that the disease is not triggered in heterozygous patients by a somatic mutation that disables the wild-type prion-protein.

Achondroplasia. Relatively many cases of homozygosity have been reported, and the phenotype is always much more severe with some resemblance to thanatophoric dwarfism. The phenotype of patients with deletions of the region 4p, including the fibroblast growth factor receptor 3 gene (*FGFR3*) (Wolf-Hirschhorn syndrome) does not result in skeletal dysplasia, therefore, achondroplasia is not caused by a loss of function. The molecular analysis of the *FGFR3* gene showed that almost all the patients with achondroplasia have the same mutation in the transmembrane domain [Rousseau et al., 1994]. This mutation is expected to have a significant effect on the ability of the transmembrane domain to form the typical α-helical structure in the lipid bilayer. In addition, it may be that the transmembrane domain plays a significant role in signal transduction, which may be altered by the mutation [Shiang et al. 1994]. Other mutations in the *FGFR3* gene cause thanatophoric dwarfism, which is clinically similar to homozygous for achondroplasia [Tavormina et al., 1995]. Therefore, the effects of mutations causing thanatophoric dwarfism in heterozygosity are similar to that of homozygosity for another mutation causing achondroplasia.

Triplet Expansions

Examples of homozygosity have been reported in Huntington disease, Machado-Joseph disease, dentatorubropallidoluysian atrophy, and myotonic dystrophy.

Huntington disease. A few homozygotes for the expansion have been reported. Comparison of age of onset, clinical presentation, and course of the disorder did not show any significant difference in heterozygous patients. Thus, it seems that this may be a true dominant gene [Wexler et al., 1987; Myers et al., 1989; The Huntington's Disease Collaborative Research Group, 1993].

Machado-Joseph disease. There have been two reports in which homozygosity was demonstrated by molecular analysis [Maruyama et al., 1995; St George-Hyslop et al., 1994]. In a large Jewish kindred from Yemen, with frequent consanguineous marriages, six homozygotes for the Machado-Joseph disease type 1 (MJD1) mutation were observed [Lerer et al., 1996]. In all homozygotes the onset was much earlier than predicted by the size of the triplet repeats alone, and the course of the disease was much more severe than in heterozygotes.

Dentatorubropallidoluysian atrophy. In one individual with dentatorubropallidoluysian atrophy (DRPLA) a relatively small expansion was found in homozygosity [Sato et al., 1995]. The onset of the disease in this patient at 17 years was much earlier than predicted by the size of the expansion.

Myotonic dystrophy. Myotonic dystrophy is caused by the expansion of a CGT repeat located in the 3′UTR of a gene encoding a putative kinase. There have been two reports in which homozygotes were confirmed by molecular studies. In one case two sisters, aged 18 and 20, respectively, were homozygotes for an expansion usually seen in minimally affected patients [Cobo et al., 1993]. The parents and the two sisters were asymptomatic even after an extensive clinical examination. In another report in which the homozygote was born from an incestuous mating between a father and his daughter [Roeder et al., 1989], the phenotype was more severe than expected by the repeat size alone. It included congenital onset of hypotonia, progressive weakness, retardation, progressive hearing loss, dysarthria, dysphagia and cardiomyopathy, and complete absence of nails. It is difficult to determine from such a report whether the clinical phenotype was related to the homozygosity only or was secondary to another genetic disorder, as may be expected in an incestuous mating. From these two reports it is difficult to conclude whether homozygosity for the myotonic dystrophy mutation leads to a phenotype that is similar or more severe than in the one observed in the heterozygote, particularly since the two asymptomatic sisters were still young, the expansion was minimal, and their parents were asymptomatic.

The three disorders—Huntington disease, DRPLA, and MJD—belong to the same category of dynamic mutations caused by amplified CAG repeats, which includes up to now three other disorders. In Huntington disease and DRPLA it was demonstrated that the polyglutamine tract is translated [Housman, 1995]. This finding is consistent with a gain of function in each gene caused by the polyglutamine-expanded stretch. The function altered by the expansion is still unknown. It has been speculated that the accumulation of the abnormal product causes progressive damage; however, no evidence for such accumulation has been found. Another possibility is that the expanded polyglutamine stretch leads to a change in the protein conformation and to a pathological interaction with other proteins [Jennings, 1995]. It may be expected then that in homozygotes the disease would be more severe than it was observed in MJD and may be also in DRPLA. The mechanisms involved are probably more complex and different in different disorders since for instance, in Huntington disease the homozygotes are affected like the heterozygotes.

CONCLUSIONS

The distinction between recessive and dominant disorders may be based only on the clinical manifestations present in the heterozygotes since in most dominant disorders the homozygotes are more severely affected

than the heterozygotes. Another way to define the inheritance may be to consider dominant inheritance as uniparental and autosomal recessive as biparental regardless of the phenotype of the heterozygotes (J. M. Opitz, personal communication). While in many cases this distinction seems arbitrary, it may be useful for clinical purposes in particular for genetic counseling. Knowledge of the molecular basis and of the possible effects of the mutations in dominant disorders helps in understanding some of the mechanisms involved in determination of the phenotype and in understanding the reasons for the more severe symptoms observed in the homozygotes.

NOTE ADDED IN PROOF

Three additional homozygous myotonic dystrophy patients have been reported [Martorell L, Illa I, Rosell J, Benitez J, Sedano MJ, Baiget M (1996): Homozygous myotonic dystrophy: Clinical and molecular studies of three unrelated cases. J Med Genet 33:783–785]. One patient had the classical form of myotonic dystrophy and the other two were mildly affected. This report confirms the observation of Cobo et al. [1993] that homozygotes do not differ from heterozygotes and that myotonic dystrophy is a true dominant disorder.

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